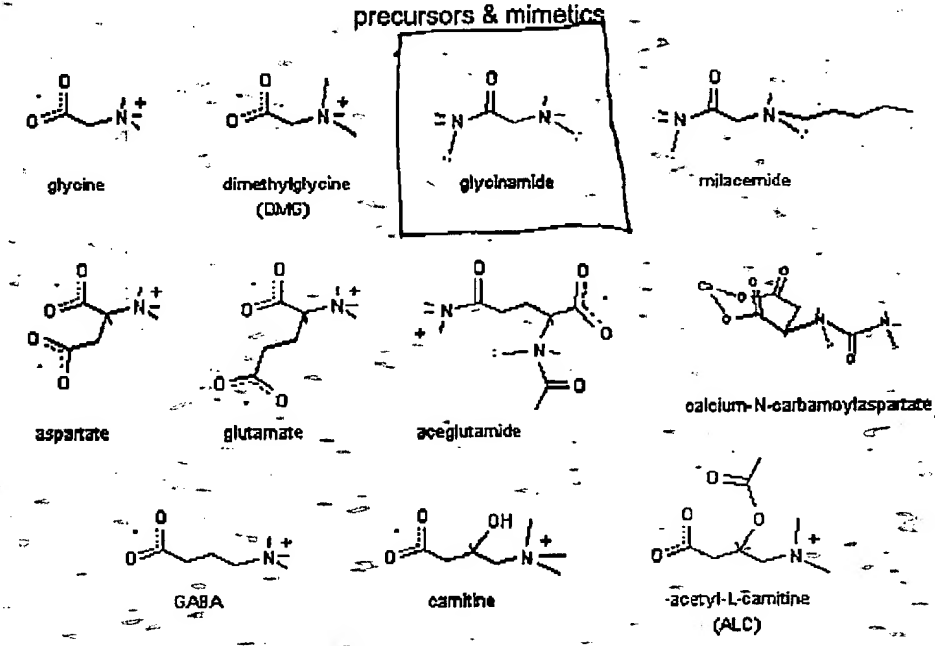
EXHIBIT A

nootropics & smart drugs

Nootropics, also known as smart drugs or cognition activators, are drugs that enhance mental function. Several mechanisms that affect nerve function may be attacked. Compounds that are used by the body to manufacture neurotransmitters constitute one group (precursors). Reuptake and degradation inhibitors form another. Mimetics of excitatory neurotransmitters and antagonists of inhibitory ones can both stimulate neural function. Antianoxics enhance the ability of neurons to burn glucose. Phospholipid compounds affect the fatty excitable membranes of nerve cells, which are responsible for transporting a depolarization pulse down dendrites and axons. Steroid compounds also affect membrane chemistry. Vasodilators which act in the CNS increase blood supply to brain cells. Still other drugs increase the flexibility of red blood cells so they can gain access to more neurons more often. All these effects be theoretically be used to enhance neurological function in the CNS.

precursors & mimetics



Glycine systems perform inhibitory functions in the CNS. Enhancement of these pathways imparts antianxiety effects and so stabilizes mood. Glycine itself is a zwitterion and so does not pass the blood-brain barrier very well. Dimethylglycine is stabilized by the methyl groups; its greater lipophilicity results in better transport to the CNS, where it is converted to glycine. Milacemide is a pro compound which decomposes (via MAO-B) to glycinamide and then glycine in the CNS.

Glutamate and aspartate are another group of excitatory neurotransmitter prominent in the CNS. Since they are acidic amino acids they have difficulty crossing the blood-brain barrier, but standard tricks can be used to deliver them to the CNS. Making an amide out of a carboxy acid is one of these (as in glutamine and aceglutamide); a somewhat more radical method is to make a covalent salt with calcium, as in calcium-N-carbamoylaspartate.

Carnitine is a catabolic (tearing-down) amino acid which serves as a neuroprotectant at NMDA receptors (a subset of glutamate/aspartate receptors). Acetylation of the hydroxy group gives ALC, which again has

EXHIBIT B

glucopyranose residues. Distributed through the cell protoplasm. Found esp in the liver and in rested muscle. Occurs also in insects and lower plants including fungi and yeasts. Isoln by alkaline destruction of the other cell constituents: Claude Bernard, *Leçons sur le diabete* (Paris, 1877) p 553; by destruction with trichloroacetic acid: Bell, Young, *Biochem. J.* 28, 882 (1934); by centrifugation: Meyer, Jeanloz, *Advan. Enzymol.* 3, 112 (1943); by hydraulic pressure: Stockhausen, Silbereisen, *Biochem. Z.* 287, 276 (1936). For biological synthesis and lysis from the Cori ester (glucose-1-phosphate) see the review and bibliography by Meyer, *Advan. Enzymol.* 3, 109 (1943); *see also* Nord, *Chem. Rev.* 26, 423 (1940); Kalckar, *ibid.* 28, 71 (1941). Isoln from the causal agent of cotton root rot, *Phymatotrichum omnivorum* (Shear) Duggar: Ergle, *J. Am. Chem. Soc.* 69, 2061 (1947). Studies on linkages: Bahl, Smith, *J. Org. Chem.* 31, 2915 (1966).

White powder. $[\alpha]_D^{25}$ +196° to +197°. Sol in water with opalescence. Insol in alc. Does not reduce Fehling's soln. With iodine, brown to violet colors are produced.

4507. Glycol Dilaurate. *Dodecanoic acid 1,2-ethanediyl ester;* ethylene dilaurate. $C_{26}H_{50}O_4$; mol wt 426.68. C 73.19%, H 11.81%, O 15.00%. $C_{11}H_{23}COOCH_2CH_2OOC-C_{11}H_{23}$.

Colorless, amorphous mass, mp 50-52°. bp_{20} 188°. Insol in alcohol, ether.

USE: In lacquers and varnishes as a plasticizer.

4508. Glycolic Acid. *Hydroxyacetic acid;* hydroxyethanoic acid. $C_2H_4O_3$; mol wt 76.05. C 31.59%, H 5.30%, O 63.11%. $HOCH_2COOH$. Constituent of sugar cane juice. Made by the action of NaOH on monochloroacetic acid; also by electrolytic reduction of oxalic acid. *Review:* Sales brochure on hydroxyacetic acid from E. I. du Pont.

Odorless, somewhat hygroscopic crystals, mp 80°. K at 25°: 1.48×10^{-4}. Soluble in water, methanol, alcohol, acetone, acetic acid, ether. pH of aq solns: 2.5 (0.5%); 2.33 (1.0%); 2.16 (2.0%); 1.91 (5.0%); 1.73 (10.0%). LD_{50} orally in rats: 1.95 g/kg, H. F. Smyth *et al., J. Ind. Hyg. Toxicol.* 23, 259 (1941).

Caution: Mild irritant to skin, mucous membranes.

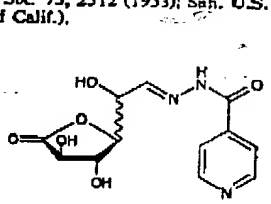
USE: In the processing of textiles, leather, and metals; in pH control, and wherever a cheap organic acid is needed, e.g. in the manuf of adhesives, in copper brightening, decontamination cleaning, dyeing, electroplating, in pickling, cleaning and chemical milling of metals.

4509. Glycol Salicylate. *2-Hydroxybenzoic acid 2-hydroxyethyl ester;* monoglycol salicylate; ethylene glycol monosalicylate; 2-hydroxyethyl salicylate; GL-7; Glysal; Norgesic; Phlogont (salve); Spirosal. $C_9H_{10}O_4$; mol wt 182.18. C 59.34%, H 5.53%, O 35.13%. $C_6H_4(OH)\cdot COOCH_2CH_2OH$.

Almost colorless, odorless liq. bp_{12} 169-172°. Soluble in about 110 parts water, 8 parts olive oil; very sol in alcohol, benzene, chloroform, ether.

THERAP CAT: Counterirritant, anti-inflammatory (topical).

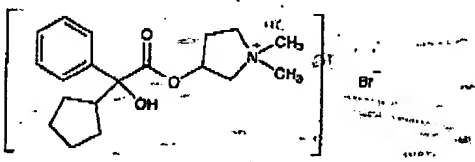
4510. Glyconiazide. *D-Glucuronic acid γ-lactone 1'-[(4-pyridinylcarboxyl)hydrazone];* D-glucuronolactone isonicotinoylhydrazone; isonicotinoylhydrazone of D-glucuronic acid lactone; isonicotinic acid hydrazide hydrazone with glucuronic acid lactone; Galatone; Gatalone; Glucazide; Gluconiazide; Gluronazide; Guidazide; Hydronsan; INH-G; Mycobactyl. $C_{12}H_{13}N_3O_6$; mol wt 295.25. C 48.82%, H 4.44%, N 14.23%, O 32.51%. Prepd by heating isonicotinic acid hydrazide with D-glucuronolactone in methanol: Sah, *J. Am. Chem. Soc.* 75, 2512 (1953); Sah, U.S. pat. 2,940,899 (1960 to U. of Calif.).



Plates and rods from methanol, needles from abs ethanol. Dec 150-160°. Freely sol in water. Practically insol in cold alc; 1.2 g dissolve in 100 ml methanol at 66°.

THERAP CAT: Antibacterial (tuberculostatic).

4511. Glycopyrrolate. *3[(Cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide; 3-hydroxy-1,1-dimethylpyrrolidinium bromide α-cyclopentylmandelate;* α-cyclopentylmandelic acid ester with 3-hydroxy-1,1-dimethylpyrrolidinium bromide; 1-methyl-3-pyrrolidyl α-cyclopentylmandelate methobromide; 1-methyl-3-pyrrolidyl α-phenyl-α-cyclopentylglycolate methobromide; 3-(2-phenyl-2-cyclopentylglycoloyloxy)-1,1-dimethylpyrrolidinium bromide; glycopyrronium bromide; AHR-504; Nodapton; Robanul; Robinul; Tarodyl; Tarodyn. $C_{19}H_{28}BrNO_3$; mol wt 398.34. C 57.29%, H 7.08%, Br 20.06%, N 3.52%, O 12.05%. Prepn: Franko; Lunsford, *J. Med. Pharm. Chem.* 2, 523 (1960); Lunsford, U.S. pat. 2,956,062 (1960 to A. H. Robins). Pharmacodynamics: E. Kaltiala *et al., J. Pharm. Pharmacol.* 26, 352 (1974). Toxicology: B. V. Franko *et al., Toxicol. Appl. Pharmacol.* 17, 361 (1970). Clinical comparison with atropine, q.v., in anaesthetic practice: F. Kongsrud, S. Sponheim, *Acta Anaesth. Scand.* 26, 620 (1982); A. I. Webb, R. M. McMurphy, *Am. J. Vet. Res.* 48, 1733 (1987); B. V. G. Malling *et al., Brit. J. Anaesth.* 60, 426 (1988). Brief review of pharmacology and clinical use: R. K. Mirakhur, J. W. Dundee, *Anaesthesia* 38, 1195-1204 (1983).

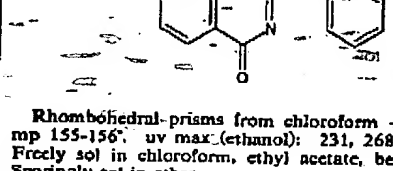


White crystals from butanone, mp 193.2-194.5°. Sol in water. LD_{50} (72 hr.) in female mice, female rats (mg/kg): 107, 196 i.p.; in male rats (mg/kg): 1150 orally (Franko).

THERAP CAT: Anticholinergic.

THERAP CAT (VET): Anticholinergic.

4512. Glycosine. *1-Methyl-2-(phenylmethyl)-4(1H)-quinazolinone;* 2-benzyl-1-methylquinazol-4-one; arborine. $C_{16}H_{16}N_2O$; mol wt 250.30. C 76.78%, H 6.64%, N 11.19%, O 6.39%. Found in the toothbrush plant, *Glycosmis pentaphylla* (Retz.) Corr., and *G. arborea* Corr., *Rutaceae.* Isoln from dried, powdered leaves: Chatterjee, Majumdar, *J. Am. Chem. Soc.* 76, 2459 (1954). Identity of arborine and glycosine, structure: Chakravarti *et al., Tetrahedron* 16, 224 (1961). Synthesis: Pakrashi *et al., Indian J. Chem.* 6, 472 (1968); Ziegler *et al., Monatsh.* 100, 948 (1969); T. Kametani *et al., Heterocycles* 9, 1585 (1978).



Rhombohedral prisms from chloroform + ethyl acetate, mp 155-156°. uv max (ethanol): 231, 268, 277, 306 nm. Freely sol in chloroform, ethyl acetate, benzene, ethanol. Sparingly sol in ether.

Hydrochloride, $C_{16}H_{14}N_2O\cdot HCl$. leaflets from 90% ethanol, dec 209-210°.

4513. *N*-Glycylglycine. $C_4H_8N_2O_3$; mol wt 132.12. C 36.36%, H 6.10%, N 21.20%, O 36.33%. $NH_2CH_2CONH-CH_2COOH$. The simplest of all peptides. Prepn from 2,5-diketopiperazine: Schott *et al., J. Org. Chem.* 12, 490 (1947); Greenstein, Winitz, *Chemistry of the Amino Acids* vol. 2, (New York, 1961) p 803. From tritylglycylglycine: Zervas *et al., J. Am. Chem. Soc.* 78, 1359 (1956). From phthalylglycylglycine: Sheehan, Frank, *ibid.* 71, 1856 (1949). From the dicyclohexylamine salt of trifluoroacetylglycylglycine: Weygand, Reiher, *Ber.* 88, 26 (1955).

Crystals from dil alc. Crys tetrahedral leaves with a lustre 264°. pK_1 3.12; pK_2 8.17. kcal/mole. Soluble in hot w Practically insol in ether.

Hydrochloride monohydrate tals from water + ethanol.

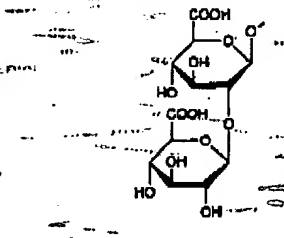
Ethyl ester hydrochloride, c 182°.

USE: In the synthesis of mo

4514. Glycyrrhiza. Lic Dried rhizome and roots of *Gly* Regel & Herder (Spanish licor *glandulifera* (Waldst. & Kit.) F rice), or of other varieties of *G.* sweet wood, *Leguminosae. Ha* tral Asia. *Constit.* 6-14% glyc cyrrhetic acid), asparagine; su the form of glycyrrhiza syrup salts.

USE: Extract and syrup as flavored vehicles).

4515. Glycyrrhizic Acid. *30-norolean-12-en-3-yl 2-O-β- copyranosiduronic acid;* glyc glycyrrhetinic acid glycoside. 61.30%, H 7.59%, O 31.11%. *glabra* L., *Leguminosae;* Karr 100 (1921); Ruzicka, Louent From commercial glycyrrhizi Cederberg, *Arch. Pharm.* 245, 122 (1937). Revised method *Clin. Med.* 47, 20 (1956). Str *Chem. Soc.* 1950, 1983. Revi *Biochem. J.* 63, 9 (1956). S *Chem. Pharm. Bull.* 36, 3710 39, 1238 (1991). *Review:* Ni (1952). Synthesis of deriva *Pharm.* 303, 905 (1970).

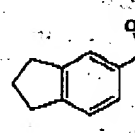


Crystals from glacial aceti $[\alpha]_D^{25}$ +46.2° (c = 1.5 in alc). hol; practically insol in ether.

Ammonium glycyrrhizinat $5H_2O$, needles from 75% aque $[\alpha]_D^{25}$ +46.9° (c = 1.5 in 40% (ε 11400). Sol in ammonia w

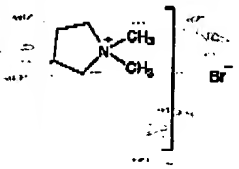
Dipotassium salt, $C_{42}H_{60}K_2$

4516. Glyhexamide. *2,3-dihydro-1H-indene-5-sul indanylsulfonyl)urea;* 1-cycl yl)urea; SQ-15860; Subose. C 59.60%, H 6.88%, N 8.69% from hydrindene-5-sulfonami Hochn, Brewer, U.S. pat. 3,(son). Clinical pharmacology *Sci.* 253, 312 (1967).



nol. needles from abs ethanol, ater. Practically insol in cold nethanol at 66°. tuberculostatic).

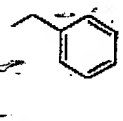
3-[(Cyclopentylhydroxyphenyl-idinium bromide; 3-hydroxy-mide α-cyclopentylmandelate; ster with 3-hydroxy-1,1-di- : 1-methyl-3-pyrrolidyl α-cy- mide: 1-methyl-3-pyrrolidyl te methobromide; 3-(2-phen-)-1,1-dimethylpyrrolidinium mide; AHR-504; Nodaptan, Tarodyn, $C_{26}H_{28}BrNO_3$; mol 18%. Br 20.06%, N 3.52%, O isford, *J. Med. Pharm. Chem.* pat. 2,956,062 (1960 to A. H. E. Kaltiala *et al., J. Pharm.* xicology: E. V. Franko *et al.,* 361 (1970). Clinical compari- esthetic practice: F. Kongs- *Scand.* 26, 620 (1982); A. L. *J. Vet. Res.* 48, 1733 (1987); *J. Anaesth.* 60, 426 (1988), and clinical use: R. K. Mi- *esia* 38, 1195-1204 (1983).



ne. mp 193.2-194.5°. Sol in le mice, female rats (mg/kg): /kg): 1150 orally (Franko).

nergic.

hyl-2-(phenylmethyl)-4(1H)- hylquinazol-4-one; arborine. 76.78%, H 5.64%, N 11.19%, brush plant, *Glycosmis pentaphylla* Corr., *Rutaceae.* Isolation Chatterjee, Majumdar. *J. Am.* dentity of arborine and glyco- *et al., Tetrahedron* 16, 224 *et al., Indian J. Chem.* 6, 472 100, 948 (1969); T. Kame- (1978).



chloroform + ethyl acetate, ol): 231, 268, 277, 306 nm. yl acetate, benzene, ethanol.

HCl, leaflets from 90% etha-

$H_8N_2O_3$; mol wt 132.12. C O 36.33%. NH_2CH_2CONH- ll peptides. Prepn from 2,5- al., *J. Org. Chem.* 12, 490 *hemistry of the Amino Acids* 3. From tritylglycylglycine: loc 78, 1359 (1956). From han, Frank, *ibid.* 71, 1856 amine salt of trifluoroacetyl- r, *Ber.* 88, 26 (1955).

Crystals from dil alc. Crystal shape described as small tetrahedral leaves with a lustrous ball in center. Dec 262-264°. pK_1' 3.12; pK_2' 8.17. Heat of combustion: 472.4 kcal/mole. Soluble in hot water; slightly sol in ethanol. Practically insol in ether.

Hydrochloride monohydrate, $C_8H_8N_2O_2.HCl.H_2O$, crystals from water + ethanol.

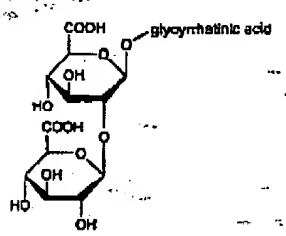
Ethyl ester hydrochloride, crystals from abs ethanol, dec 182°.

USE: In the synthesis of more complicated peptides.

4514. Glycyrrhiza. –Licorice; liquorice; sweet root. Dried rhizome and roots of *Glycyrrhiza glabra* L., var. *typica* Regel & Herder (Spanish licorice), or of *G. glabra* L., var. *glandulifera* (Waldst. & Kit.) Regel & Herder (Russian licorice), or of other varieties of *G. glabra* yielding a yellow and sweet wood. *Leguminosae. Habit.* Southern Europe to Central Asia. *Constit.* 6-14% glycyrrhizin (the glucoside of glycyrrhetic acid), asparagine, sugars, resin. Used chiefly in the form of glycyrrhiza syrup. *Incompat.* Acids, metallic salts.

USE: Extract and syrup as pharmaceutic aids (flavor and flavored vehicles).

4515. Glycyrrhizic Acid. *(3β,20β)-20-Carboxy-11-oxo-30-norolean-12-en-3-yl 2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid;* glycyrrhizin; glycyrrhizinic acid; glycyrrhetinic acid glycoside. $C_{42}H_{62}O_{16}$; mol wt 822.94. C 61.30%, H 7.59%, O 31.11%. Extraction from *Glycyrrhiza glabra* L., *Leguminosae;* Karrer, Chao. *Helv. Chim. Acta* 4, 100 (1921); Ruzicka, Lowenberger, *ibid.* 19, 1402 (1936). From commercial glycyrrhizinum ammoniacale: Tschirch, Cederberg. *Arch. Pharm.* 245, 97 (1907); Voss *et al., Ber.* 70, 122 (1937). Revised method of isoln: Conn, Conn. *J. Lab. Clin. Med.* 47, 20 (1956). Structure: Lythgoe, Trippett, *J. Chem. Soc.* 1950, 1983. Revised structure: Marsh, Levvy, *Biochem. J.* 63, 9 (1956). See also: I. Kitagawa *et al., Chem. Pharm. Bull.* 36, 3710 (1988); T. Hatano *et al., ibid.* 39, 1238 (1991). *Review:* Nieman, *Chem. Weekbl.* 48, 213 (1952). Synthesis of derivatives: Brieskorn, Sax, *Arch. Pharm.* 303, 905 (1970).

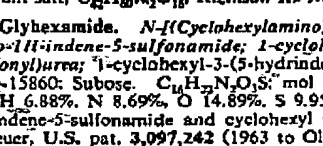


Crystals from glacial acetic acid. Intensely sweet taste. $[\alpha]_D^{27}$ +46.2° (c = 1.5 in alc). Freely sol in hot water, alcohol; practically insol in ether.

Ammonium glycyrrhizinate pentahydrate, $C_{42}H_{65}NO_{16}.5H_2O$, needles from 75% aqueous ethanol, decomp 212-217°. $[\alpha]_D^{20}$ +46.9° (c = 1.5 in 40% ethanol). uv max: 248 nm (ε 11400). Sol in ammonia water, glacial acetic acid.

Dipotassium salt, $C_{42}H_{60}K_2O_{16}$. *Rizinsan K2 A2.*

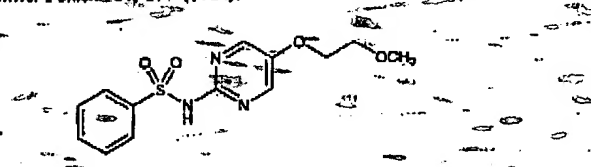
4516. Glyhexamide. *N-[(Cyclohexylamino)carbonyl]-2,3-dihydro-1H-indene-5-sulfonamide; 1-cyclohexyl-3-(5-indanylsulfonyl)urea;* SQ-15860; Subose. $C_{16}H_{22}N_2O_3S$; mol wt 322.43. C 59.60%, H 6.88%, N 8.69%, O 14.89%, S 9.95%. Prepd from hydrindene-5-sulfonamide and cyclohexyl isocyanate: Hoehn, Breuer, U.S. pat. 3,097,242 (1963 to Olin Mathieson). Clinical pharmacology: Grinnell *et al., Am. J. Med. Sci.* 253, 312 (1967).



Crystals from 70% acetone, mp 153-155°.

THERAP CAT: Antidiabetic.

4517. Glynidine. *N-[5-(2-Methoxyethoxy)-2-pyrimidinyl]benzenesulfonamide;* 2-benzenesulfonamido-5-(β-methoxyethoxy)pyrimidine; glycodiazine. $C_{13}H_{15}N_3O_4S$; mol wt 309.35. C 50.48%, H 4.89%, N 13.58%, O 20.69%, S 10.37%. Prepn: Belg. pat. 609,270; H. Priewe *et al.,* U.S. pat. 3,275,635 (1962, 1966 both to Schering, AG); Gütsche *et al., Arzneimittel-Forsch.* 14, 373 (1964). Series of articles on pharmacology: *ibid.* 377-412. Activity: Losert *et al., ibid.* 23, 1251 (1973). Metabolism: Soyfer *et al., Chim. Ther.* 5, 441 (1970). Toxicity data: Kramer *et al., Arznei-mittel-Forsch.* 14, 377 (1964).

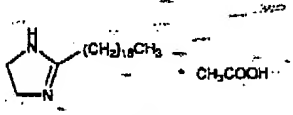


Crystals, mp 152-154°. Soly in ethanol: 0.91%; in toluene: 0.67%.

Sodium salt, $C_{13}H_{14}N_3NaO_4S$. *SH-717, Glyconormal, Gondafon, Lycanol, Redul.* Crystals, mp 221-226°. Sparingly sol in alc. Soly in water at 37°: 70.5%. LD_{50} in mice, rats (g/kg): 1.48, 2.00 i.v.; 5.30, 2.85 orally (Kramer).

THERAP CAT: Antidiabetic.

4518. Glyodin. *2-Heptadecyl-4,5-dihydro-1H-imidazole monoacetate;* 2-heptadecylglyoxalidine acetate; Crag Fruit Fungicide 341. $C_{22}H_{44}N_2O_2$; mol wt 368.60. C 71.69%, H 12.03%, N 7.60%, O 8.68%. Prepn from stearic acid and ethylenediamine: Kiff, U.S. pat. 2,540,171 (1951 to Union Carbide and Carbon).



Light orange crystals, mp 62-68°. d^{20} 1.035. Insol in water, acetone, toluene. Sol in isopropanol.

Base, soft greasy wax, mp 94°.

USE: Agricultural fungicide.

4519. Glyoxal. *Ethanedial;* biformyl; diformyl; oxalaldehyde. $C_2H_2O_2$; mol wt 58.04. C 41.39%, H 3.47%, O 55.14%. OHCCHO. Prepd by the oxidation of acetaldehyde by nitric or selenious acid: Lubawin, *Ber.* 8, 768 (1875); Wyss, *Ber.* 10, 1366 (1877); Küllm, *Ann.* 416, 230 (1918); Riley *et al., J. Chem. Soc.* 1932, 1881; Ronzio, Waugh, *Org. Syn.* coll. vol. III, 438 (1955); by hydrolysis of dichlorodioxane: Butler, Cretcher, *J. Am. Chem. Soc.* 54, 2988 (1932). Review of commercial development: J. F. Bohmfalk *et al., Ind. Eng. Chem.* 43, 286 (1951). Toxicity study: H. F. Smyth *et al., J. Ind. Hyg. Toxicol.* 23, 259 (1941). *Review:* A. B. Boese *et al.,* in *Glycols,* G. O. Curme, F. Johnston, Eds. (Reinhold, New York, 1952) pp 125-128.

Yellow prisms or irregular pieces turning white on cooling. d^{20} 1.14. Opaque at 10°, mp 15°. bp_{776} 51°. The vapors are green and burn with a purple flame. *Explosive:* Mixtures with air may explode! $n_D^{18.5}$ 1.3826. Sol in anhydr solvents. pH of a 40% aq soln: 2.1-2.7; d_4^{20} 1.27. Polymerizes quickly on standing, on contact with water (violent reaction), or when dissolved in solvents contg water. The anhydr polymer changes to the monomer on heating. Solns of the monomer are obtained on heating the polymer with anethole, phenetole, safrole, methyl nonyl ketone, or benzaldehyde. LD_{50} in rats, guinea pigs (mg/kg): 2020, 760 orally (Smyth).

Dihydrate, $(OHCCHO)_2.2H_2O$, crystalline powder, nonhygroscopic. More sol in hot water than in cold water. Commercially available in anhydr form as crystalline dihydrate, or as a 40% aq soln which may contain polymerization inhibitors.